Drugs - Real World Outcomes (2016) 3:289–296
DOI 10.1007/s40801-016-0080-7

CrossMark

ORIGINAL RESEARCH ARTICLE

Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults

Meghan K. Mattos[1] · Susan M. Sereika[1,2] · Jennifer G. Naples[3] · Steven M. Albert[4]

Published online: 21 June 2016

Abstract

Background Older adults are especially susceptible to adverse consequences of potentially inappropriate medications (PIMs), such as benzodiazepine receptor agonists (BZDRAs), due to age-related pharmacokinetic and pharmacodynamic changes. Although some risk factors for BZDRA use in older adults have been identified, the role of rural versus urban residence is less clear.

Objective To describe BZDRA use in rural versus urban older adults using pharmaceutical claims from Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) program.

Methods The sample consisted of older adults enrolled in Pennsylvania's *Healthy Steps for Older Adults* and participated in Pennsylvania's PACE program. Independent sample *t* tests and contingency tables were used to examine residence differences. Multivariate binary logistic modeling was performed.

Results The total sample ($N = 426$) was 305 (71.6 %) urban-dwelling adults and 121 (28.4 %) rural-dwelling adults. Rural participants were more likely to be male, white, married, and have less than a high school education compared with urban participants ($p < .01$). Specifically, 25 % of rural-dwelling adults received a BZDRA compared with 15 % of urban-dwelling adults ($p = 0.02$). Three variables reached statistical significance for predicting BZDRA use in a multivariate model: rural residence (OR 2.58, 95 % CI 1.39–4.79), history of anxiety/depression (OR 4.20, 95 % CI 2.39–7.46), and number of medications (OR 1.11, 95 % CI 1.02–1.21).

Conclusions BZDRA prescription differences in older, rural-dwelling adults further highlights the need for geriatric and mental health specialists to provide specialized care to this population. Rural healthcare professionals may be less aware of PIMs for older adults, and initiatives to support geriatric services and provide education for existing providers may be beneficial.

Key Points

25 % of older, rural-dwelling adults received a benzodiazepine receptor agonist compared with 15 % of urban-dwelling older adults based on Pennsylvania's Pharmaceutical Assistance Contract for the Elderly program claims data ($p = 0.02$).

Rural residence, history of anxiety/depression, and total medication count predicted use of benzodiazepine receptor agonists.

✉ Meghan K. Mattos
mkm65@pitt.edu

1 Department of Health and Community Systems, University of Pittsburgh School of Nursing, 415 Victoria Building, 3500 Victoria Street, Pittsburgh, PA 15261, USA

2 Departments of Health and Community Systems, Epidemiology, and Biostatistics, University of Pittsburgh School of Nursing, Graduate School of Public Health, and Clinical Translational Science Institute, 360 Victoria Building, 3500 Victoria Street, Pittsburgh, PA 15261, USA

3 Division of Geriatric Medicine, University of Pittsburgh School of Medicine, 3471 Fifth Avenue, Kaufmann Building, Suite 500, Pittsburgh, PA 15213, USA

4 Behavioral and Community Health Sciences, University of Pittsburgh Graduate School of Public Health, 208 Parran Hall, Pittsburgh, PA 15261, USA

1 Introduction

Potentially inappropriate medications (PIMs) are those medications where risks associated with their use outweigh possible benefits [1]. Due to pharmacokinetic and pharmacodynamic changes associated with aging, older adults are especially susceptible to the adverse consequences of PIMs [2]. The repercussions of this increased sensitivity may be readily seen with benzodiazepine receptor agonists (BZDRAs), which include both traditional benzodiazepines and the non-benzodiazepine receptor agonist sleep aids of zolpidem, eszopiclone, and zaleplon (commonly known as "Z" drugs"). BZDRAs have been associated with serious adverse events in the elderly, including cognitive impairment, delirium, falls, fractures, and motor vehicle crashes [3, 4].

Despite mounting information regarding these adverse consequences, use of BZDRAs in older adults has remained constant over the previous decade [7]. Recent studies estimate that between 12 and 32 % of older adults receive a benzodiazepine, with rates exceeding 50 % in those older adults with depression or anxiety [8]. Moreover, older adults are more likely to receive benzodiazepines for longer periods (i.e., ≥120 days) than their younger counterparts [9]. Similarly, a nationally representative survey found that approximately one-third of all prescriptions for non-benzodiazepine BZDRA sleep aids from 1993–2010 were for adults ≥65 years old [10]. Sleep aids, particularly "Z" drugs, are considered inappropriate in older adults, specifically because of possible drug-disease interactions in the elderly. BZDRAs, including the "Z" drugs, have been associated with cognitive impairment, and there is recent evidence that suggests a possible link with dementia, although this relationship needs to be further delineated [5, 6].

Although some risk factors for inappropriate BZDRA use in older adults have been identified, the role of rural versus urban residence is less clear. Recently, Edelstein et al. [11] reported that older adults residing in rural Pennsylvania were 1.5 times as likely ($p = 0.045$) to use anxiolytics (e.g., benzodiazepines) and nearly twice as likely ($p = 0.33$) to use sedative-hypnotics (i.e., non-benzodiazepine receptor agonist sleep aids) than their urban counterparts. However, medication use data in this study were derived from participant self-report, which may increase the likelihood of exposure misclassification compared with more objective measures of medication utilization. Therefore, the purpose of this study was to describe BZDRA use in rural versus urban older adults using pharmaceutical claims data from Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) program. It was hypothesized that older, rural-dwelling adults would be more likely to use BZDRAs compared to their urban counterparts.

2 Methods

2.1 Study Design

This correlational study was a secondary analysis of data collected for Falls-Free PA, a research study comparing falls incidence among older adults completing Pennsylvania's *Healthy Steps for Older Adults* ($n = 814$) and a comparison group of older adults who did not complete the program but attended the same senior centers offering *Healthy Steps* ($n = 1015$). Details of the design and outcomes of *Falls Free PA* have been reported previously [12]. After providing informed consent, participants completed baseline interviews and received monthly follow-up phone calls for a year. The University of Pittsburgh Institutional Review Board approved the parent study.

2.2 Sample

The sample for this secondary analysis was older adults enrolled in Pennsylvania's *Healthy Steps for Older Adults* program between 2010 and 2011 who also participated in Pennsylvania's PACE program during that time ($N = 426$). Falls-Free PA enrolled subjects from 19 counties from *Healthy Steps* senior center sites between 2010 and 2011. All subjects completed baseline interviews after providing informed consent and received monthly follow-up phone calls for up to a year. Inclusion criteria were: 50 years of age or older and attending PA Department of Aging programs at *Healthy Step* sites. Exclusion criteria were inability to provide informed consent, language spoken other than English or Spanish, and inability to participate in telephone follow-up calls. Additional information and details regarding recruitment and follow-up are available [11, 13]. Eligibility criteria for PACE include: 65 years of age or older; Pennsylvania residence for at least 90 days prior to date of application; not being currently enrolled in Department of Public Welfare's Medicaid prescription benefits; and last calendar year's income for a single person being ≤US$14,500 or, for a married couple, a combined income ≤US$17,700. The PACE Annual Report for 2011 showed 134,255 Pennsylvanians were enrolled in PACE from 2010 to 2011 [14, 15].

2.3 Measures

2.3.1 Descriptive Variables

Sociodemographic variables included age (in completed years) as a continuous variable and gender (male/female), race (white/non-white), marital status (married/ not married), living situation (living with someone/not living with someone), and education (less than high school [HS]/any HS/ beyond HS) as categorical variables. Medical conditions were coded as binary variables (yes/no) in response to the question, "Has a doctor ever told you that you had (a)…" and included 17 medical conditions. The total number of prescription medications (up to 15 medications) was self-reported at baseline [12].

2.3.2 Urban Rural Classification

Rural-Urban Continuum Codes from the US Department of Agriculture system were used to determine urban and rural residence based on county of residence [16]. Similar to the original paper by Edelstein et al. [11], we used population size to create a dichotomous location variable: urban (counties with $\geq$250,000 residents) or rural (counties with $<$250,000 residents).

2.3.3 Exposure Classification

Given their similar mechanisms of action and adverse risk profiles, benzodiazepines and non-benzodiazepine receptor sleep aids were grouped into one exposure category [3]. Relevant medications were identified by a clinical geriatric pharmacist (JN) according to explicit criteria [3]: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, eszopiclone, flurazepam, lorazepam, oxazepam, quazepam, temazepam, triazolam, zaleplon, and zolpidem. Any BZDRA use was categorized as "yes" if the participant received at least one BZDRA per PACE claims data during enrollment in the study. PACE maintains a prospective drug utilization review to ensure "safe and effective use of medications," including reviewing safety issues related to the medications and communicating with patient's physicians [17].

2.3.4 Predictors of Benzodiazepine Receptor Agonist (BZDRA) Use

Predictors were chosen *a priori* based on a comprehensive review of the literature to identify potential confounders that may influence benzodiazepine use, including sociodemographic characteristics (i.e., age, education, gender, race, and marital status), history of anxiety/depression, and total number of medications [18–21].

2.4 Analysis

Statistical analyses were conducted using IBM® SPSS® Statistics v.23 (IBM Corporation, Armonk, NY, USA). Exploratory analyses were first employed for the screening for any data anomalies, including outliers and missing data. Missing data were analyzed by both amount and pattern. Only seven participants (1.6 %) had missing data on one variable used in analysis. We also examined for patterns of missing data and found that data were missing completely at random (MCAR) using Little's MCAR test [$\chi^2(7) = 9.74$, $p = 0.20$]. No imputation was performed, as they appeared to be a random subset of the study sample. Thus, the seven participants with missing data were omitted in the final analysis. Descriptive statistics were calculated as means and standard deviations for continuous variables and frequencies and percentages for categorical variables for the total sample and by rural/urban residence for all sociodemographic variables, medical conditions (individual and total), total number of medications, and BZDRA use. Differences between types of residence were assessed using independent sample *t* tests for continuous variables and contingency tables with chi-square tests of independence (or Fisher's Exact tests if cells were sparsely populated) for categorical variables. Binary logistic regression modeling was performed to examine *a priori* predictors of benzodiazepine receptor agonist use, as well as possible interactions between predictor variables for these outcomes. Adjusted odds ratios (ORs) with 95 % confidence intervals (CIs) were estimated from full multivariate binary logistic regression models, where identified covariates were adjusted for, and ultimately contained all predictors of interest. A stepwise approach was also used to confirm findings. Level of statistical significance was set at $<$0.05 for two-sided hypothesis testing.

3 Results

The total sample ($N = 426$) was comprised of 305 (71.6 %) urban-dwelling older adults and 121 (28.4 %) rural-dwelling older adults. As seen in Table 1, rural participants were more likely to be male, white, married, and less likely to have more than a high school education when compared to their urban counterparts ($p < 0.01$). On average, rural-dwelling older adults also reported taking more total medications at baseline than urban-dwelling older adults (4.95 $\pm$ 3.31 medications vs. 4.21 $\pm$ 3.04 medications, respectively, $p = 0.03$). Specifically, 25 % of rural-dwelling older adults received a BZDRA, compared to 15 % of urban-dwelling older adults ($p = 0.02$). There were no differences between rural and urban participants with regard to age, living situation, medical conditions, self-

Table 1 Baseline characteristics of Falls-Free Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) participants ($N = 426$)

Characteristic	Total sample	Residence		*p* value
		Rural (*n* = 121)	Urban (*n* = 305)	
Sociodemographics				
Age (years), mean ± standard deviation (SD)	79.16 ± 6.72	79.81 ± 6.41	78.90 ± 6.83	0.21
Female, *n* (%)	378 (88.7)	95 (78.5)	283 (92.8)	*<0.01*
White[a], *n* (%)	388 (91.3)	119 (98.3)	269 (88.2)	*<0.01*
Married[b], *n* (%)	44 (10.3)	23 (19.0)	21(6.9)	*<0.01*
Lives with someone[b], *n* (%)	108 (25.5)	33 (27.3)	75 (24.8)	0.59
Education, *n* (%)				*<0.01*
Less than high school	86 (20.2)	30 (24.8)	56 (18.4)	
Any high school	244 (57.3)	78 (64.5)	166 (54.4)	
Beyond high school	96 (22.5)	13 (10.7)	83 (27.2)	
Medical conditions[c]				
Anxiety or depression, *n* (%)	98 (23.1)	30 (22.4)	68 (25.0)	0.56
Arthritis, *n* (%)	299 (70.7)	84 (70.6)	215 (70.7)	0.98
Cancer, *n* (%)	84 (19.8)	29 (24.2)	55 (18.1)	0.16
Cognitive impairment/ problems with memory, *n* (%)	20 (4.7)	4 (3.3)	16 (5.3)	0.39
Congestive heart failure, *n* (%)	36 (8.6)	12 (10.2)	24 (8.0)	0.48
COPD or asthma, *n* (%)	61 (14.4)	16 (13.3)	45 (14.8)	0.70
Diabetes, *n* (%)	122 (28.8)	42 (35.0)	80 (26.4)	0.08
Fracture after age 50 years, *n* (%)	117 (27.7)	25 (21.0)	92 (30.3)	0.06
Glaucoma, *n* (%)	46 (10.9)	14 (11.7)	32 (10.6)	0.74
Heart attack, *n* (%)	43 (10.2)	17 (14.3)	26 (8.6)	0.08
High blood pressure, *n* (%)	321 (75.9)	97 (80.8)	224 (73.9)	0.13
Inner ear problem, *n* (%)	68 (16.2)	22 (18.8)	46 (15.2)	0.37
Macular degeneration, *n* (%)	59 (14.0)	17 (14.3)	42 (13.9)	0.92
Numbness in feet/ peripheral neuropathy, *n* (%)	81 (19.2)	29 (24.4)	52 (17.2)	0.09
Osteoporosis, *n* (%)	127 (30.5)	35 (29.9)	92 (30.8)	0.87
Parkinson disease, *n* (%)	3 (0.7)	1 (0.8)	2 (0.7)	1.00[d]
Stroke, *n* (%)	56 (13.2)	17 (14.2)	39 (12.8)	0.71
Total number of medications, mean ± SD	4.42 ± 3.13	4.95 ± 3.31	4.21 ± 3.04	*0.03*
Benzodiazepine receptor agonist use, *n* (%)	77 (18.1)	30 (24.8)	47 (15.4)	*0.02*

COPD chronic obstructive pulmonary disease

[a] *n* = 425

[b] *n* = 424

[c] All medical conditions are in response to the question, "Has a doctor ever told you that you had (a)…"

[d] Fisher's Exact test was used due to cells with expected counts less than 5

Italicised p-values indicate statistical significance ($p < 0.05$)

reported anxiety/depression, or total number of self-reported medical conditions.

Using multivariate binary logistic regression considering all predictor variables, the full model demonstrated a good fit [$\chi^2_{\text{H-L}}(8) = 4.70$, $p = 0.79$] and three predictors were identified as significantly independently associated with BZDRA use: rural residence (OR 2.58, 95 % CI 1.39–4.79), history of anxiety/depression (OR 4.22, 95 % CI 2.39–7.46, and total number of medications (OR 1.11, 95 % CI 1.02–1.21) (Table 2). These results suggest that rural residents had 2.58 times the odds of BZDRA use compared to urban residents; and those participants with a history of anxiety or depression had 4.20 times the odds of BZDRA use compared to participants without a history of anxiety or depression. For each additional medication used, the odds of using a BZDRA increased by 11 %. Based on forward stepwise regression, the same three predictor variables were retained in the parsimonious model for BZDRA use. Odds ratios, confidence limits, and significance values were similar in both models.

Table 2 Multivariate binary logistic regression analysis of predictors of benzodiazepine receptor agonist use ($N = 419$)

Predictor	Adjusted odds ratio (95 % confidence interval)
Age (years)	1.026 (0.982–1.073)
Residence	
Urban ($n = 301$)	1.000
Rural ($n = 118$)	2.579 (1.387–4.794)**
Education	
Less than high school ($n = 83$)	1.000
Any high school ($n = 241$)	1.135 (0.543–2.372)
Beyond high school ($n = 95$)	1.645 (0.679–3.985)
Gender	
Male ($n = 47$)	1.000
Female ($n = 372$)	1.707 (0.661–4.407)
Race	
White ($n = 382$)	1.000
Black ($n = 37$)	0.351 (0.076–1.614)
Marital status	
Married ($n = 43$)	1.000
Not married ($n = 376$)	0.973 (0.376–2.523)
Anxiety or depression	
No ($n = 286$)	1.000
Yes ($n = 133$)	4.219 (2.386–7.459)***
Total number of medications	1.111 (1.021–1.208)*

* $p < 0.05$, ** $p < 0.005$; *** $p < 0.001$

4 Discussion

This study is among the first to examine the association of rural versus urban residence and benzodiazepine use in a population of older adults. Overall, this study found that prevalence of BZDRA use was higher in rural-dwelling, older Pennsylvania adults compared with their urban counterparts, at 25 and 15 %, respectively. Previously, Edelstein et al. [11] evaluated the rate of anxiolytic and sedative-hypnotic use among participants included in *Healthy Steps for Older Adults* using medication self-report and found that 8 % of rural dwelling older adults and 5 % of urban-dwelling older adults used BZDRAs. The present study combined data for participants enrolled in both *Healthy Steps for Older Adults* and the Pennsylvania Pharmaceutical Contract for Assistance for the Elderly (PACE) program. Rates of BZDRA use captured using PACE claims data were higher than those detected using self-report; however, the magnitude of the difference was similar.

These findings are consistent with previous studies that suggest that rural residents may be at increased risk for inappropriate prescribing [22–24]. Specifically, Lund et al. [24] found that rural Veterans in the South and Northeast (including Pennsylvania) were more likely to receive inappropriate medications, which included certain BZDRAs. Rural residence has previously been associated with challenges accessing health services [25]. However, the rates of use of BZDRAs detected in the current study reflect ready access to *inappropriate* medications. As such, it is possible that the frequency of use is a reflection of decreased access to high-quality, geriatric-focused care services, including non-pharmacologic interventions such as psychotherapy [24, 26].

In addition to urban versus rural residence, it is not surprising that participants with a history of depression or anxiety were four times as likely to receive a BZDRA as these medications are frequently used to treat psychiatric and sleep disorders. Indeed, this is nearly identical to the fivefold increased risk identified in another recent study evaluating benzodiazepine use among older adults in the community [7]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine uptake inhibitors (SNRIs) are considered a more appropriate treatment for people with a history of anxiety and/or depression. We found that in our study sample, only 11.3 % if the total sample reported SSRI use (9.5 % urban and 15.7 % rural) and 2.1 % reported SNRI use (2.3 % urban and 1.7 % rural). Although anxiety and depression are primary indicators for SSRI or SNRI use, there was fairly low reported use of these medications when compared to the BZDRA use observed (15–25 %). The lower prevalence of these indicated antidepressants and higher BZDRA prevalence further points to inappropriate prescribing in this population.

It is also important to note that, to date, benzodiazepines have not been shown effective in treating depression. Although benzodiazepines are effective in treating anxiety, they are generally not preferred due to adverse drug profile and addiction potential as well as availability of equally efficacious and safer alternatives. It is noteworthy that we did not find differences between rural and urban participants with a history of depression or anxiety that may help explain the differences seen in BZDRA use. This may be a combination of rural areas having fewer healthcare providers, limited health services, and possibly missed or incorrect diagnoses by rural providers [27, 28].

Polypharmacy has also been consistently identified as a predictor of inappropriate medication prescribing [20]. In our study, the odds of BZDRA use increased by 11 % for each additional medication received. Applying this finding to an older adult receiving four medications, as per a recent study [29], this represents a 48 % cumulative increased odds of BZDRA use compared with an individual taking no medications. We did not find any of the sociodemographic variables to be significant predictors of BZDRA use, and this may be due to small sample sizes for certain groups within variables (e.g., male/ gender and black/ race).

The rates of BZDRA use among community-dwelling older adults identified in this study are consistent with recent literature. For example, in one study using data from the National Ambulatory Medical Care Survey, 12 % of older adults visiting ambulatory care clinics received a benzodiazepine [7]. Moreover, these rates seem to be rising, especially among the oldest old (i.e., $\geq$85 years old) [7]. Importantly, between 30 and 50 % of older adults use benzodiazepines chronically [9, 18]. Given the serious repercussions of BZDRA on cognition (e.g., delirium) and mobility (e.g., falls, fractures) in the elderly, the high rates of BZDRA use detected in this study—especially among rural dwellers—represents a target for quality improvement interventions [3]. It is important to note that although PACE maintains a prospective drug utilization review to evaluate possible medication safety issues, this review does not serve as a comprehensive review of all patients' medical conditions and indications for medication use [17]. Advantages of having both a single primary-care provider and pharmacy reviewing all current medication types, uses, dosages, and frequencies is ideal for providing streamlined medication review and ensuring safety for the patient. In a recent Cochrane Review examining psychosocial interventions for BZDRA use, abuse, or independence [30], cognitive behavioral therapy (CBT) plus BZDRA taper more effectively reduced BZDRA use compared to taper alone over 3 months. Although this intervention for short-term BZDRA use reduction is encouraging, reduced use was not sustained at 6 months. Thus, CBT plus taper should be encouraged in both urban and rural older adults; however, there should be an emphasis on seeking specialty geriatric and psychiatric providers to help maintain a BZDRA-free medication regimen in this population.

Some strengths of the current study were BZDRA prescription measurement, large sample size, older sample, and collaboration with PACE. Prescription medication use by participants was not self-report, which may have provided more accurate reports, especially in this older sample taking multiple medications. Additionally, 21.3 % of Pennsylvania's population lives in rural areas, and this secondary analysis was able to retain a fairly high number of rural participants for inclusion (14.1 % of the entire sample). Based on the current literature, this study is the first of its kind to use data from participants in the PACE program to explore benzodiazepine receptor agonist prescriptions with an emphasis on differences between rural and urban settings.

As with any observational study, some limitations should be noted. This was a descriptive study, and consequently there was no determination whether this discrepancy between rural and urban residence resulted in meaningful differences in adverse events. Additionally, frequency and duration of use were not available. Therefore, the authors were unable to calculate dose and cumulative exposure, which may be more important when considering health outcomes such as hip fracture. Another limitation is that non-pharmacologic interventions, such as psychotherapy, where not collected from participants at baseline and, therefore, were not considered in analysis. It may be that non-pharmacologic interventions to treat conditions BZDRAs are being prescribed for are less available in rural areas compared to urban areas. Additionally, it would have been ideal to have additional data about diagnosis or history of insomnia for participants as this may have provided further explanation for BZDRA use and/or the relationship with depression.

Generalizability for the study may also be limited, as only Pennsylvanians in lower socioeconomic classes were captured when Falls Free PA and PACE databases were combined. However, the rates identified in the current study are similar to a previously-published study of benzodiazepine use in older adults receiving governmental prescription assistance, with 25 % of older adults receiving benzodiazepines [31]. Moreover, though the sample was predominately White, female, and married, there were statistically significant differences noted between rural and urban groups.

5 Conclusion

This study confirms that rural residence may be an important risk factor for BZDRA use. As with any medication, healthcare providers must weigh the benefits and possible side effects of a medication prior to prescribing, and the decision to prescribe BZDRAs in older, rural-dwelling adults further highlights the need for geriatric and mental health specialists to provide specialized care to this population. Because healthcare professionals in rural settings may be less aware of PIMs for older adults, initiatives to support geriatric services, provide education for existing providers, and improve prescribing in this setting may yield beneficial results for older adults.

Acknowledgments The authors would like to thank Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) for providing medication claims data through a data sharing agreement.

Author contributions Meghan K. Mattos, Jennifer G. Naples, Susan M. Sereika, and Steven M. Albert contributed to the development process leading up to the manuscript, drafted and/or revision of the manuscript, and approved the final submitted version of the manuscript.

Compliance with Ethical Standards

Conflict of interest Meghan K. Mattos, Jennifer G. Naples, and Susan M. Sereika have no conflicts of interest to declare. Steven M. Albert served as principal investigator on the Centers for Disease Control and Prevention grant supporting this research.

Funding Research supported by cooperative agreement DP002657 and Prevention Research Centers program (U48 DP001918) from the Centers for Disease Control and Prevention, and by NIH AG024827, Pittsburgh Older Americans Independence Center. The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the views of the National Institutes of Health.

References

1. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, Hanlon JT. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370(9582):173–84.
2. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6–14.
3. Fick DM, Semla TP, Beizer J, Brandt N, Dombrowski R, DuBeau CE, Eisenberg W, Epplin JJ, Flanagan N, Giovannetti E, Hanlon J, Hollmann P, Laird R, Linnebur S, Sandhu S, Steinman M. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
4. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med. 2003;163: 2716–24.
5. Pariente A, de Gage SB, Moore N, Bégaud B. The benzodiazepine-dementia disorders link: current state of knowledge. CNS Drugs. 2016;30(1):1–7.
6. Gray SL, Dublin S, Yu O, Walker R, Anderson M, Hubbard RA, Crane PK, Larson EB. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. BMJ 2016;352:i90.
7. Marra EM, Mazer-Amirshahi M, Brooks G, van den Anker J, May L, Pines JM. Benzodiazepine prescribing in older adults in U.S. Ambulatory Clinics and Emergency Departments (2001–10). J Am Geriatr Soc. 2015;63(10):2074–81.
8. Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. Br J Psychiatry. 2014;204(2):98–107.
9. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015;72(2):136–42.
10. Kaufmann CN, Spira AP, Alexander GC, Rutkow L, Mojtabai R. Trends in prescribing of sedative-hypnotic medications in the USA: 1993–2010. Pharmacoepidemiol Drug Saf. 2016;25(6): 637–45.
11. Edelstein O, Pater K, Sharma R, Albert S. Influence of urban residence on use of psychotropic medications in Pennsylvania, USA: cross-sectional comparison of older adults attending senior centers. Drugs Aging. 2014;31(2):141–8.
12. Albert SM, King J, Boudreau R, Prasad T, Lin CJ, Newman AB. Primary prevention of falls: effectiveness of a statewide program. Am J Public Health. 2014;104(5):e77–84.
13. Albert S, Edelstein O, King J, Flatt J, Lin CJ, Boudreau R, Newman AB. Assessing the quality of a nonrandomized pragmatic trial for primary prevention of falls among older adults. Prev Sci. 2015;16(1):31–40.
14. Paulus RM, Barlow L, Shughart DL, Butler B, Brown TV. PACE annual report 2011, Harrisburg, 2011.
15. PACE, PACENET, and PACE Plus Medicare, PACE and Affordable Medications, 2014. Online. Available: http://www.portal.state.pa.us/portal/server.pt/community/pace_and_affordable_medications/17942. Accessed 08 Aug 2014.
16. USDA Economic Research Service—Rural-Urban Continuum Codes. Online. Available: http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx#.UjXCPZV8tuo. Accessed 15 Sep 2013.
17. Pharmaceutical Assistance Contract for the Elderly. Annual Report to the Pennsylvania General Assembly, Harrisburg, 2010.
18. Kurko TA, Saastamoinen LK, Tähkäpää S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, Airaksinen MS, Hietala J. Long-term use of benzodiazepines: definitions, prevalence and usage patterns—a systematic review of register-based studies. Eur Psychiatry. 2015;30(8):1037–47.
19. Fourrier A, Letenneur L, Dartigues JF, Moore N, Bégaud B. Benzodiazepine use in an elderly community-dwelling population. Characteristics of users and factors associated with subsequent use. Eur J Clin Pharmacol. 2001;57(5):419–25.
20. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1): 57–65.
21. Guzman JS, Sohn L, Harada ND. Living alone and outpatient care use by older veterans. J Am Geriatr Soc. 2004;52(4):617–22.

22. Stuart B, Kamal-Bahl S, Briesacher B, Lee E, Doshi J, Zuckerman IH, Verovsky I, Beers MH, Erwin G, Friedley N. Trends in the prescription of inappropriate drugs for the elderly between 1995 and 1999. Am J Geriatr Pharmacother. 2003;1(2):61–74.
23. Aparasu RR, Sitzman SJ. Inappropriate prescribing for elderly outpatients. Am J Heal Pharm. 1999;56(5):433–9.
24. Lund BC, Charlton ME, Steinman MA, Kaboli PJ. Regional differences in prescribing quality among elder veterans and the impact of rural residence. J Rural Health. 2013;29(2):172–9.
25. Lund BC, Abrams TE, Bernardy NC, Alexander B, Friedman MJ. Benzodiazepine prescribing variation and clinical uncertainty in treating posttraumatic stress disorder. Psychiatr Serv. 2013;64(1):21–7.
26. Peterson LE, Bazemore A, Bragg EJ, Xierali I, Warshaw G. Rural-urban distribution of the U.S. Geriatrics physician workforce. J Am Geriatr Soc. 2011;59(4):699–703.
27. Gamm L, Hutchison L, Bellamy G, Dabney BJ. Rural healthy people 2010: identifying rural health priorities. J Rural Health. 2002;18(1):9-14.
28. Barley GE, Reeves CB, O'Brien-Gonzales A, Westfall JM. Characteristics of and issues faced by rural female family physicians. J Rural Heal. 2001;17(3):251–8.
29. Charlesworth CJ, Smit E, Lee DSH, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. J Gerontol. 2015;70(8):989–95.
30. Darker Catherine D, Sweeney Brion P, Barry Joe M, Farrell Michael F. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev. 2015;5:CD009652.
31. Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, Ross-Degnan D. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med. 2004;164(14):1567–72.